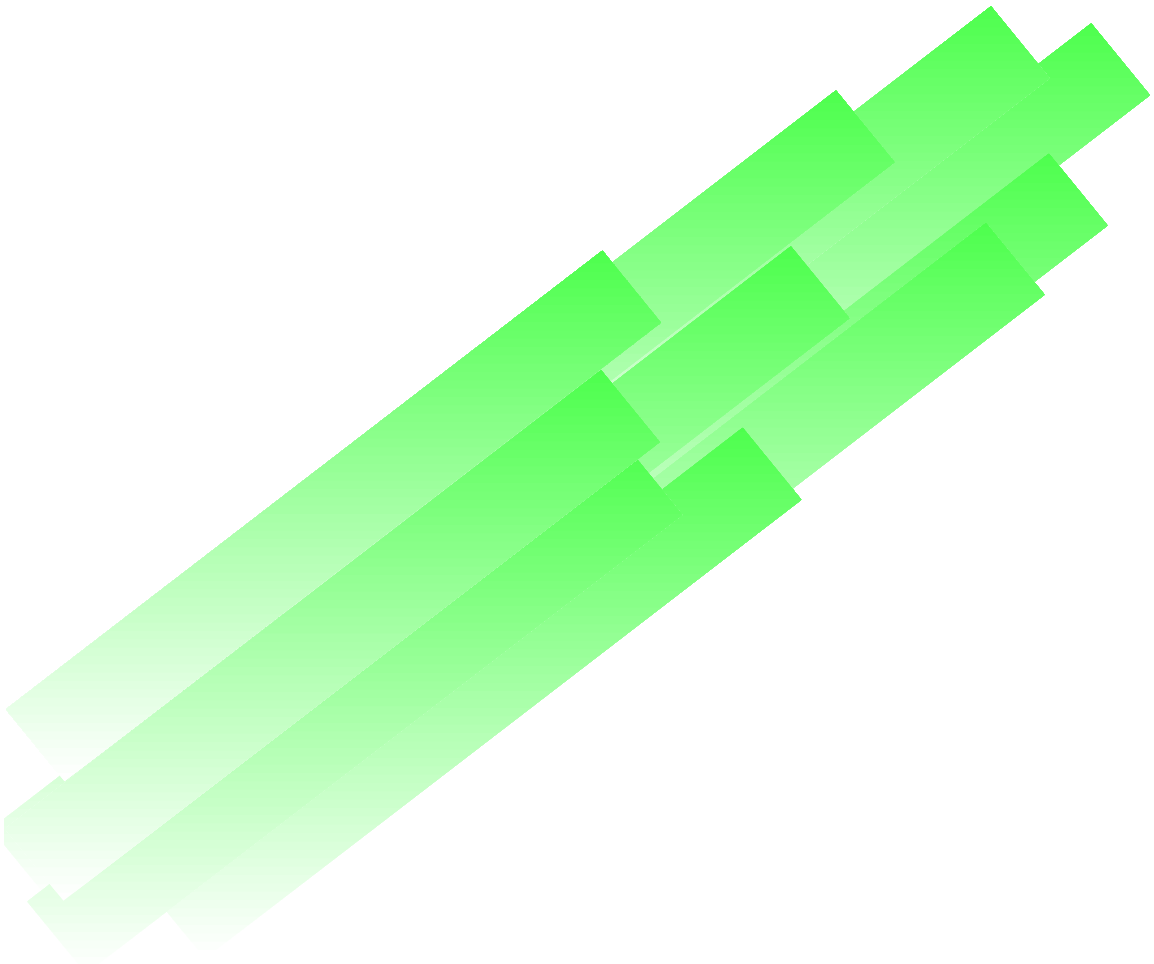
Guidance for Industry

Labeling Guidance for Risperidone Tablets



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Additional copies are available from:

Office of Generic Drugs
Division of Labeling and Program Support
Labeling Review Branch
Attention: Team Leader
MetroPark North II
7500 Standish Place, Room 266N
Rockville, MD 20855-2773

(Tel) 301-827-5846
(Internet) http://www.fda.gov/cder/guidance/index.htm

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GUIDANCE FOR INDUSTRY[1]

Labeling Guidance for Risperidone Tablets

I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (RISPERDAL®; Janssen Pharmaceutica; 20-272/S-004; Approved February 28, 1996; Revised February 1996). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

RISPERIDONE TABLETS

DESCRIPTION

Risperidone is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-piperidin]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido(1,2-*a*)pyrimidin-4-one. Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. Its structural formula is as follows:

[INSERT STRUCTURAL FORMULA HERE]

Each tablet for oral administration contains, __ mg risperidone. In addition, each tablet contains the following inactive ingredients:

[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter ,1091> for guidance).]

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[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of risperidone, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2(D_2) and serotonin type 2($5HT_2$) antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of risperidone.

Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2($5HT_2$), dopamine type 2(D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. Risperidone antagonizes other receptors, but with lower potency. Risperidone has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is *N*-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 mg to 16 mg daily (0.5 mg to 8 mg BID). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6% to 8% of caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma

concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5 to 6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \approx 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS - Drug Interactions).

The plasma protein binding of risperidone was about 90% over the *in vitro* concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL) and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

RENAL IMPAIRMENT: In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

HEPATIC IMPAIRMENT: While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone

in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ELDERLY: In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE AND ADMINISTRATION).

RACE AND GENDER EFFECTS: No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of risperidone in the management of the manifestations of psychotic disorders was established in three short-term (6 to 8 week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6 week, placebo-controlled trial (n=160) involving titration of risperidone in doses up to 10 mg/day (BID schedule), risperidone was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8 week, placebo-controlled trial (n=513) involving 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 risperidone groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest risperidone dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and

there was no suggestion of increased benefit from larger doses.

(3) In an 8 week, dose comparison trial (n=1356) involving 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest risperidone dose groups were generally superior to the 1 mg risperidone dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

INDICATIONS AND USAGE

Risperidone tablets are indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of risperidone was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of risperidone in long-term use, that is, more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use risperidone tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Risperidone tablets are contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, risperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on risperidone, drug discontinuation should be considered. However, some patients may require treatment with risperidone despite the presence of the syndrome.

Potential for Proarrhythmic Effects

Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12 to 16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

ORTHOSTATIC HYPOTENSION: Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of risperidone treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 1 mg BID in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medication.

SEIZURES: During premarketing testing, seizures occurred in 0.3% (9/2607) of risperidone treated patients, two in association with hyponatremia. Risperidone should be used cautiously in patients with a history of seizures.

HYPERPROLACTINEMIA: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (See PRECAUTIONS - *CARCINOGENESIS*). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

POTENTIAL FOR COGNITIVE AND MOTOR IMPAIRMENT: Somnolence was a commonly reported adverse event associated with risperidone treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of risperidone 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

PRIAPISM: Rare cases of priapism have been reported. While the relationship of the events to risperidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP): A single case of TTP was reported in a 28 year-old female patient receiving risperidone in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to risperidone therapy is unknown.

ANTIEMETIC EFFECT: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

BODY TEMPERATURE REGULATION: Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

SUICIDE: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for risperidone should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

USE IN PATIENTS WITH CONCOMITANT ILLNESS: Clinical experience with risperidone in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using risperidone in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Risperidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were

excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received risperidone and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking risperidone whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe risperidone:

ORTHOSTATIC HYPOTENSION: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE: Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

PREGNANCY: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

NURSING: Patients should be advised not to breast feed an infant if they are taking risperidone.

CONCOMITANT MEDICATION: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

ALCOHOL: Patients should be advised to avoid alcohol while taking risperidone.

Laboratory Tests
No specific laboratory tests are recommended.

Drug Interactions
The interactions of risperidone and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when risperidone is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

Risperidone may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

DRUGS THAT INHIBIT CYTOCHROME $P_{450}IID_6$ AND OTHER P_{450} ISOZYMES: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers ($n \approx 70$) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

DRUGS METABOLIZED BY CYTOCHROME $P_{450}IID_6$: *In vitro* studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility
CARCINOGENESIS: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg)	
			LOWEST EFFECT LEVEL	**HIGHEST NO EFFECT LEVEL**
Pituitary adenomas	mouse	female	0.75*(9.4)*	0.2*(2.4)*
Endocrine pancreas adenomas	rat	male	1.5*(9.4)*	0.4*(2.4)*
Mammary gland adenocarcinomas	mouse	female	0.2*(2.4)*	none
	rat	female	0.4*(2.4)*	none
Mammary gland neoplasms, Total	rat	male	6*(37.5)*	1.5*(9.4)*
	rat	male	1.5*(9.4)*	0.4*(2.4)*

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS - General).

MUTAGENESIS: No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

IMPAIRMENT OF FERTILITY: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m^2 basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m^2 basis. Dose-related decreases were

also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy
TERATOGENIC EFFECTS, PREGNANCY CATEGORY C: The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to risperidone therapy is unknown.

Risperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of Risperidone on labor and delivery in humans is unknown.

Nursing Mothers
It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in breast milk. Therefore, women receiving risperidone should not breast feed.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of risperidone did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of risperidone-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	Risperidone	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of risperidone treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in risperidone compared to placebo patients, it is unlikely that suicide attempt is a risperidone related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Commonly Observed Adverse Events in Controlled Clinical Trials

In two 6 to 8 week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the risperidone groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing risperidone at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug- related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More among Risperidone Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among risperidone treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8 week controlled trials. Patients received risperidone doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of

patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2 mg, 6 mg, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

TABLE 1:

Treatment-Emergent Adverse Experience Incidence in 6 to 8 week Controlled Clinical Trials[1]

Body System/Preferred Term	**Risperidone** ≤10 mg/day (N=324)	16 mg/day (N=77)	**Placebo** (N=142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%

Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1]Events reported by at least 1% of patients treated with risperidone ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for risperidone 16 mg/day and placebo are provided as well. Events for which the risperidone incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of "extrapyramidal symptoms" does not appear to differ for the "≤ 10 mg/day" group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (See ADVERSE REACTIONS - Dose Dependency of Adverse Events).

Dose Dependency of Adverse Events

EXTRAPYRAMIDAL SYMPTOMS: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8 week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8 week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

OTHER ADVERSE EVENTS: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

VITAL SIGN CHANGES: Risperidone is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

WEIGHT CHANGES: The proportions of risperidone and placebo-treated patients meeting a weight gain criterion of $\geq$7% of body weight were compared in a pool of 6 to 8 week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for risperidone (18%) compared to placebo (9%).

LABORATORY CHANGES: A between group comparison for 6 to 8 week placebo-controlled trials revealed no statistically significant risperidone/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no risperidone/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, risperidone administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG CHANGES: The electrocardiograms of approximately 380 patients who received risperidone and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking risperidone whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-marketing Evaluation of Risperidone
During its premarketing assessment, multiple doses of risperidone were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to risperidone varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the listings that follow).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of risperidone who experienced an event of the type cited on at least one occasion while receiving risperidone. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with risperidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

PSYCHIATRIC DISORDERS: *Frequent*: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent*: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare*: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS: *Frequent*: increased sleep duration*. *Infrequent*: dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare*: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

GASTRO-INTESTINAL DISORDERS: *Frequent*: anorexia, reduced salivation*. *Infrequent*: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare*: fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue

discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

BODY AS A WHOLE/GENERAL DISORDERS: *Frequent*: fatigue. *Infrequent*: edema, rigors, malaise, influenza-like symptoms. *Rare*: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

RESPIRATORY SYSTEM DISORDERS: *Infrequent*: hyperventilation, bronchospasm, pneumonia, stridor. *Rare*: asthma, increased sputum, aspiration.

SKIN AND APPENDAGE DISORDERS: *Frequent*: increased pigmentation*, photosensitivity*. *Infrequent*: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare*: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

CARDIOVASCULAR DISORDERS: *Infrequent*: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare*: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

VISION DISORDERS: *Infrequent*: abnormal accommodation, xerophthalmia. *Rare*: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

METABOLIC AND NUTRITIONAL DISORDERS: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare*: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

URINARY SYSTEM DISORDERS: *Frequent*: polyuria/polydipsia*. *Infrequent*: urinary incontinence, hematuria, dysuria. *Rare*: urinary retention, cystitis, renal insufficiency.

MUSCULO-SKELETAL SYSTEM DISORDERS: *Infrequent*: myalgia. *Rare*: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

REPRODUCTIVE DISORDERS, FEMALE: *Frequent*: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent*: nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

LIVER AND BILIARY SYSTEM DISORDERS: *Infrequent*: increased SGOT, increased SGPT. *Rare*: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

PLATELET, BLEEDING AND CLOTTING DISORDERS: *Infrequent*: epistaxis, purpura.

Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

HEARING AND VESTIBULAR DISORDERS: *Rare*: tinnitus, hyperacusis, decreased hearing. *RED BLOOD CELL DISORDERS*: *Infrequent*: anemia, hypochromic anemia. *Rare*: normocytic anemia.

REPRODUCTIVE DISORDERS, MALE: *Frequent*: erectile dysfunction*. *Infrequent*: ejaculation failure.

WHITE CELL AND RESISTANCE DISORDERS: *Rare*: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

ENDOCRINE DISORDERS: *Rare*: gynecomastia, male breast pain, antidiuretic hormone disorder.

SPECIAL SENSES: Rare: bitter taste.

*Incidence based on elicited reports.

POSTINTRODUCTION REPORTS: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to risperidone therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving risperidone. A causal relationship with risperidone has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Risperidone is not a controlled substance.

Physical and Psychologic Dependence

Risperidone has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of risperidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute risperidone overdosage with estimated doses ranging from 20 mg to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged OT, and widened ORS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute risperidone overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to risperidone overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to risperidone. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose

Risperidone should be administered on a BID schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a

target dose of 3 mg BID by the third day. In some patients, slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 mg BID are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of risperidone, however, maximal effect was generally seen in a range of 4 to 6 mg/day. Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations
The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS).

Maintenance Therapy
While there is no body of evidence available to answer the question of how long the patient treated with risperidone should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on risperidone, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued
Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off risperidone, the initial titration schedule should be followed.

Switching from Other Antipsychotics
There are no systematically collected data to specifically address switching from other antipsychotics to risperidone, or concerning concomitant administration with other

antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, if medically appropriate, initiate risperidone therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring
  Note: The innovator's tablets are scored as follows:
  1 mg - **SCORED**
  2 mg, 3 mg and 4 mg **UNSCORED**
- Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light and moisture.
- "Dispense in" statement - Dispense in a tight light-resistant container as defined in the USP.
- "Caution: Federal Law..." statement.

Include the following information at the end of the HOW SUPPLIED section:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name should read as follows:

  Risperidone Tablets

- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.